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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
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SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,518	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/7/06; 11/14/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7,8,17,19-21,23,24,28,29,31-34 and 38-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7,8,17,19-21,23,24,28,29,31-34 and 38-55* is/are rejected.

7)☒ Claim(s) *1, 17, 21, and 34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 11/14/06 and 12/7/06. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, and 31-34 have been amended, claims 3-6, 9-16, 18, 22, 25-27, 30, and 35-37 have been canceled, and claims 38-55 have been added. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, and 38-55 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Interview Record

2. The interview record is complete (see interview summary filed by applicant 11/14/06).

Election/Restrictions

3. The restriction applied to different disease types is WITHDRAWN. While the inventions remain distinct as previously set forth, given the nature of the disclosures of the references applied in this office action, there is not serious burden on the examiner which would justify maintaining the restriction.

Priority

4. The claims have basis in the parent application, except for claims which are rejected in this office action for having new matter relative to the instant application. These claims do not have support in the parent. A full analysis to determine if the claims have support from an enablement perspective in the parent application has not been undertaken because there is no relevant intervening art.

Claim Objections

5. Claim 1 is objected to because of the following informalities: As amended the claim reads "...diagnosing or prognosing a disease a test subject...". The deletion of the word "in" from between "disease" and "a" appears to be an error.

6. Claim 17 is objected to because it recites "of blood samples which have 'no' been fractionated" in line five of the claim. It appears the word "no" was used where the word "not" was intended.

7. Claim 21 is objected to because it recites "an amplification products" which does not have proper plural agreement between singular an and plural products.

8. Claim 34 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 34 is objected to insofar as it depends from claim 1, which already requires that the control subjects do not have said disease.

9. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. Claim 17, 20, 23, 28, 29, 33, 34, 39, 40, 41, 43, 46, and 49 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite because it recites that each of said genes is identified "as a further marker of said disease" yet no marker was identified as the first marker within the claim. It is

confusing what it means for the gene to be a "further" marker. All claims which depend from claim 17 are also indefinite over this recitation.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 39 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

Claim 39 requires that "subjects having said disease" in the methods for identifying markers of claims 7, 8, 17, or 19, "have no overt symptoms with respect to said disease." Claim 46 includes a limitation which appears to be new matter, namely the recitation that "the subjects having said disease are asymptomatic with respect to said disease." These generic claims encompasses the selection of markers in any possible disease. The remarks filed with the amendment points out that there is descriptive support in ¶79 of the specification for the limitation "said subjects having said disease are asymptomatic with respect to said disease" (Paragraph number refers to the numbering in PGPUB US2004/0014059 which is the publication of the parent application). This paragraph clearly teaches that the methods disclosed can be used "for monitoring a patient for the onset of overt symptoms of a disease," but is silent as to a method which uses patients that are asymptomatic for a disease as a means for identifying

markers for a disease. Applicant argues that the examiner is requiring a burden that is greater than the requirement of 112 1st paragraph. However, the examiner disagrees, and maintains that she is merely looking to the specification for a written description of the invention as claimed.

The specification provides a single example where differential expression of insulin between control patients, diabetic patients, and a person having asymptomatic diabetes is detected (Example 6, see top of page 36). However, the specification does not provide any discussion of how the disclosed methods could be applied to any patient asymptomatic for any disease. In the case of "asymptomatic diabetes" this is somewhat of a misnomer because in order to in fact determine a patient as being within this class, some symptoms of diabetes must be present. In any case, it is agreed that there is one specific example of determining if a gene transcript may be a marker for diabetes using patients who are "asymptomatic" for diabetes who have diabetes.

The claim is sufficiently broad so as to make this application to any disease, and the claim requires that "said patient HAVING said disease is asymptomatic for said disease." Applicant argues in the remarks that the analysis of ZFP in the specification demonstrates using a patient who is asymptomatic for a disease to look for possible markers for a disease. Namely, using patients who have diabetes but have not been diagnosed with cardiac hypertrophy or heart failure to look for a potential marker for cardiac hypertrophy and/or heart failure. The claim requires that the patients have the disease but are asymptomatic. The specification, in the ZFP example, does not teach that these diabetes patients HAVE cardiac hypertrophy and/or heart failure but are asymptomatic, as required by the claim. The specification generally suggests that the increased levels of ZFP "may indicate that these subjects are headed in that general direction

(¶0058)." Thus, the specification suggests that these subjects may develop the disease, not that they have the disease, as required by the claims. There is no discussion of patients who are "asymptomatic" for heart failure but have heart failure. It is not even clear to the examiner that one could HAVE heart failure but be asymptomatic for heart failure. The specification does not generally describe or discuss the use of asymptomatic patients for marker identification for any or all diseases, as encompassed by the instant claim, and so this claim is rejected for new matter because the breadth of the claim does not appear to be contemplated in the instant specification.

13. Claims 1, 2, 32, 44, 45, 47, and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 20, 21, 23, 24, 28, 29, 31, 33, 34, 38, 41, and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein one of these claims depends from claims 7, 8, 17 or 19, does not reasonably provide enablement for methods wherein they depend from methods of diagnosis or prognosis as set forth in claims 1 and/or 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejected claims are drawn to method for diagnosing or prognosing a disease via the analysis of expression of two or more genes that are detected in RNA from a blood sample wherein the blood sample has not been fractionated into cell types, and wherein a difference between the quantified level of expression in a sample subject versus the level of RNA

determined in control subjects diagnoses or prognoses a disease. The clear language of the claim is that the determination of a difference in step (c) results in diagnosing or prognosing a disease in a test subject. Dependent claim 43 specifically sets forth that the disease is selected from colorectal cancer, diabetes, and heart failure.

The nature of the invention, therefore, requires the knowledge of minimal sets of "two or more genes" is whose differential expression between a sample and a control is sufficient to determine that a disease is present or to predict the outcome of a disease.

The specification teaches methods for identifying markers that are differentially expressed in the blood of patients versus controls, and establishes that blood samples that have not been fractionated into cell types can be assayed and genes which are differentially expressed between diseased individuals and controls can be identified. This is embodied in the claimed invention as "methods for identifying markers." Claims drawn to identifying markers are not within the scope of this rejection. For a number of disease (coronary artery disease, obesity, hypertension, diabetes, hyperlipidemia, lung disease, bladder cancer, rheumatoid arthritis, depression, and osteoartiritis) applicant has showed that differentially expressed genes can be identified, identifying hundreds to thousands of such genes. The specification fails to teach, however, for most of these genes if they are up or down regulated in diseased versus control samples. The specification does not undertake any further analysis to determine which pairs of two genes are sufficient to reliably determine the presence of disease (that is to DIAGNOSE disease) or which pairs of two genes are predictive of the outcome and/or recovery of an individual's disease course. The specification does not provide any guidance as to which sets of two or more genes are uniquely over or under expressed in any disease, such that their

differential expression relative to a control is sufficient to diagnose or prognose disease. The specification does teach any differentially expressed genes related to colorectal cancer or heart failure, per se, such that these genes would be clear choices for diagnosis of the diseases.

An enormous amount of experimentation and validation would be required to practice the claimed invention using only the guidance given in the specification. One would have to sift through the lists of hundreds or thousands of genes given for the diseases analyzed to determine which of the gene pairs are sufficient to diagnose any one of the diseases. On would have to then undertake further experimentation to validate and confirm the diagnostic utility of the methods. While the instant specification provides a beginning means to identify markers for disease that may be useful for in strategies to diagnose disease, the instant claims reach through the method for finding markers to a method which is not supported by the specification. For the prognosis aspect of the claims, a long term study in which one tests gene expression and then follows patients as their diseases progress to determine if there is a reliable association between gene expression in blood and disease progression exists would be required. Only if such an association can be established could one use the claimed invention for analysis of progression.

Furthermore, the unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (2001). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis.

Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The analysis and experimentation required to go from the teachings in the specification is extensive and in a highly unpredictable technology area.

Thus, having carefully considered all of these factors, it is concluded that it would require undue experimentation to practice the claimed invention for diagnosis or prognosis of disease.

14. Claim 43 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to the diagnosis or prognosis of colorectal cancer, diabetes, or heart failure by the detection of expression of two or more genes. The practice of the claimed invention requires written description of methods which utilize minimally two or more genes to diagnose or prognose one of these diseases.

The specification does not provide any written description of genes for diagnosis of colorectal cancer. The specification teaches 915 genes that are differentially expressed in diabetic patients versus healthy controls, but the specification does not describe which pairs of two or more are sufficient to determine the presence of disease or to predict outcome of disease. The specification provides genes that are differentially expressed in patients that have coronary artery disease and hypertension but does not provide written description of genes that are diagnostic of heart failure, per se.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No common structural attributes identify the members of the genus of genes whose differential expression within the claimed methods results in "thereby diagnosing or prognosing said disease." The current methods set forth in the current claims encompass the detection of a large genus of "two or more genes" that may be differentially expressed in the blood of subject and control patients. This large genus is represented in the specification by not a single member in the case of colorectal cancer and heart failure, and for diabetes nearly a thousand possible genes are represented, but there is no written description as to which of those pairs of "two or more" are sufficient to accomplish the goals set forth in the claims. The general knowledge and

level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure in the specification alone is insufficient to describe the genus. The general knowledge in the art concerning differential expression does not provide any indication of any structural features that might be common to all genes that might function in the claimed methods. Common attributes are not described. The specification provides no correlation between structure of differentially expressed genes and the function of such genes within the claimed methods. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 103

15. Claims 7, 8, 20, 21, 23, 24, 28, 29, 31, 33, 34, 38, 40, 42, 49, 52, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ringel et al. (Journal of Clinical Endocrinology and Metabolism, Vol. 83, Number 12, pages 4435-4442) in view of Kinoshita et al. (Analytical Biochemistry, Volume 206, Issue 2, 1 November 1992, pages 231-235).

Ringel et al. teach a method for identifying a marker useful for diagnosing residual and recurrent thyroid cancer said method comprising using thyroglobulin primers (which are oligonucleotides of predetermined sequence and are also primers specific only for cDNA complementary to thyroglobulin RNA) to detect the presence of thyroglobulin transcript in total

RNA that was isolated from blood samples of patients having thyroid cancer and normal patients (p. 4436). Since total RNA was isolated, this meets the claim limitations which set forth that the RNA is "of blood samples which have not been fractionated into cell types." Ringel et al. teach that thyroglobulin RNA was detected in the blood all tested "normal" subjects, thus expressly teaching that this gene is a gene expressed in blood tissue of a subject not having thyroid cancer (p. 4438). Thyroglobulin is also expressed in the thyroid gland.

Regarding claims 20, 21, 38 said RNA is detected by generating and detecting a cDNA (which is an EST) derived from said RNA, and said cDNA is produced with gene specific primers via RT-PCR on extracted RNA.

Regarding claims 33, 40, and 42 the subjects are human.

Regarding claim 34, the "normal" subjects do not have thyroid cancer.

Regarding claim 49, Ringel et al. teach assaying subjects with and without metastatic thyroid cancer, and comparing their thyroglobulin expression (p. 4438).

Regarding claims 52 and 53 isolate of total RNA from cells necessarily requires lysis of the cells.

Ringel et al. teach that "Quantitation of thyroglobulin mRNA detection will be needed for serial measurements in patients to identify disease progression which is required for optimal utility of the assay (p. 4441)."

Ringel et al. test samples from diseased and control patients and compare the outcomes, but Ringel et al. do not quantify and compare the level of RNA encoded by thyroglobulin in the disease and normal samples.

At the time the invention was made, methods for quantifying mRNA in a sample and comparing test and control samples were well known in the prior art. For example, Kinoshita et al. teach quantification of gene expresssion using RT-PCR, and teach that their method is highly sensitive for evaluating gene expression over a wide range (abstract and thoughout). The method taught by Kinoshita et al. includes steps of using oligonucleotides of predetermined sequence, namely primers specific for only complementary to a specific gene, and quantifying the level of said RNA encoded by the sample. Furthermore, Kinoshita et al. teach a method wherien quantifiying the level of RNA is effected by determining a quantity realtive to the housekeeping gene beta-actin, thus teaching the step set forth in claims 28, 29, and 31 (abstract and throughout).

Therefore, at the time the invention was made, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method taught by Ringel et al. so as to have used methods for quantifying and comparing gene expression of a specific transcript present in two samples as exemplified by Kinoshita et al. One would have been motivated to modify Ringel et al. by the express suggestion of Ringel et al. to apply quantitative analysis to their research directed at identifying a marker useful for diagnosing thyroid cancer. In view of the cited references, the claimed invention is prima facie obvious. Regarding claims 23 and 24 comparison of the normal and diseased subjects would necessarily include quantifying said control RNA amplificaiton products, as suggested by Ringel et al.

16. Claims 7, 8, 20, 21, 23, 24, 28, 29, 31, 33, 34, 38, 40, 42, 52, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagai et al. in view of Kephart (Promega Notes Magazine, Number 62, p. 11-15, 1997).

Regarding claim 7, Nagai et al. teach a method comprising the steps of detecting the presence of RNA encoded by a gene expressed in blood and in non-blood tissue of a subject not having said disease in a sample of whole blood from each of one or more subjects having said disease, and quantifying a level of said RNA in said sample and determining a difference between said level and a quantified level of control RNA from an sample of whole blood from each of one or more first control subjects, said control RNA being encoded by said gene and being detectable in said sample from said control subjects, said difference identifying said gene as a marker of said disease. Namely, Nagai et al. teach the detection of the D3 dopamine recteptor in the peripheral blood of patients with Parkinson's disease and in the blood of healthy controls (p. 791), and teach that patients with disease have lower expression of the receptor than controls, and that this difference is significant between the two populations (p. 792-793). Nagai et al. complete their analysis using RT-PCR, and thus produce amplificaiton products from the sujbects, as required in claim 8. Regarding claims 52 and 53, isolation of RNA results in the lysis of cells.

Regarding claims 20, 21, 38, and 42, the expression is generated by detecting and cDNA/EST producted with gene specific primers via RT-PCR on extracted RNA.

Regarding claims 23, 28, 29, and 31, the expression of test and control D3 receptor is compared to the housekeeping gene beta-actin (p. 791-793).

Regarding claim 24, Nagai et al. quantify the level of amplificaiton product from the control subjects, and Nagai et al. run the amplificaiton products onto a gel, which isolates the control RNA (p. 792).

Regarding claims 33 and 40, the subjects are human.

Regarding claim 34, the control subject does not have Parkinson's disease.

The teachings of Nagai et al. do not teach detection of gene expression in a blood sample which has not been fractionated into cell types, as Nagai et al. detect RNA in lymphocytes.

Kephart teaches a method for rapid isolation of RNA from small quantities of human whole blood for RT-PCR analysis. Kephart teaches "techniques routniely used to purify RNA from blood require relatively large quantities of starting material to isolate peripheral blood cells prior to extraction," and instead provide methods to isolate RNA from whole blood (p. 11).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Nagai et al. so as to have avoided the step of isolating lymphocytes using a method as taught by Kephart. One would have been motivated to modify the methods taught by Nagai et al. as taught by Kephart in order to avoid the need to isolate the blood cells, and to utilize the systems taught by Kephart since Kephart teaches that they "enable quick and simple RNA preparation that can be completed in 20-120 minutes, and are appropriate for high-throughput analysis of both RNA and DNA species present in small numbers of white blood cells, serum or whole blood samples (p. 14)." Thus, at the time the invention was made, the claimed invention was prima facie obvious.

17. Claims 1, 2, 7, 8, 17, 19, 20, 21, 23, 24, 28, 29, 31, 32, 33, 34, 38, 40, 41, 42, 44, 45, 47, 48, 50, 51, 52, 53, 54, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (British Journal of Cancer (1997) 76(5) 628-633) in view of Kephart (Promega Notes Magazine, Number 62, p. 11-15, 1997).

Regarding claim 7, Wong et al. teach a method comprising the steps of detecting the presence of RNA encoded by a gene expressed in blood and in non-blood tissue of a subject not

having said disease in a sample of whole blood from each of one or more subjects having said disease, and quantifying a level of said RNA in said sample and determining a difference between said level and a quantified level of control RNA from an sample of whole blood from each of one or more first control subjects, said control RNA being encoded by said gene and being detectable in said sample from said control subjects, said difference identifying said gene as a marker of said disease. Namely, Wong et al. teach the detection of the albumin mRNA and alpha-fetoprotein mRNA recteptor in the peripheral blood of patients with hepatocellular carcinoma and in the blood of healthy controls (p. 629-631), and teach that patients with disease have higher expression of both of these genes, and that this difference is significant between the two populations (figures 3 and 4). Wong et al. complete their analysis using RT-PCR, and thus produce amplificaiton products from the sujbects, as required in claim 8. Regarding claims 1, 2, 50, and 51, Wong et al. teach using the quantitiative differential expression assay as a means for quantifying HCC cells and predicting the formation of metastasis in patients who have not been diagnosed with metastatic disease (i.e. have not been diagnosed with disease) (p. 633). Thus, the markers are markers of progression of HCC to metastatic disease. Regarding claims 17, 19, 50, 51, 54 and 55, Wong et al. analyze a set of "two or more" genes. Regarding claims 50-55, the isolation of RNA results in the lysis of cells.

Regarding claims 20, 21, 38, 41, and 42, the expression is generated by detecting and cDNA/EST producted with gene specific primers via RT-PCR on extracted RNA.

Regarding claims 23, 28, 29, and 31, the expression of test and control mRNA is compared to the housekeeping gene beta-microglobulin (p. 630).

Regarding claim 24, Wong et al. quantify the level of amplificaiton product from the control subjects (p. 629-630).

Regarding claims 32, 33 and 40, the subjects are human.

Regarding claim 34, the control subject does not have hepatocellular carcinoma disease.

The teachings of Wong et al. do not teach detection of gene expression in a blood sample which has not been fractionated into cell types, as Wong et al. detect RNA in peripherial mononuclear cells (p. 629).

Kephart teaches a method for rapid isolation of RNA from small quantities of human whole blood for RT-PCR analysis. Kephart teaches "techniques routniely used to purify RNA from blood require relatively large quantities of starting material to isolate peripheral blood cells prior to extraction," and instead provide methods to isolate RNA from whole blood (p. 11).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Wong et al. so as to have avoided the step of isolating lymphocytes using a method as taught by Kephart. One would have been motivated to modify the methods taught by Wong et al. as taught by Kephart in order to avoid the need to isolate the blood cells, and to utilize the systems taught by Kephart since Kephart teaches that they "enable quick and simple RNA preparation that can be completed in 20-120 minutes, and are appropriate for high-throughput analysis of both RNA and DNA species present in small numbers of white blood cells, serum or whole blood samples (p. 14)." Furhtermore, it would have been obvious to have applied this screening to patients with HCC who do not have overt symptoms of metastatic disease in order to provide a means for diagnosing metastatic

disease early for earlier treatment. Thus, at the time the invention was made, the claimed invention was prima facie obvious.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, and 38-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims

1-17 and 22 of copending Application No. 11/313302. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application either anticipate or make obvious on their face the claims of the instant application. The claims of the copending application provide methods for identifying biomarkers based on differential expression of RNA transcripts expressed in blood of patients having disease or not having disease compared to the other, as is claimed in the instant application. The claims of the copending application further provide methods for diagnosis and prognosis based upon such markers (see claim 17 therein). The claims of the copending application are silent as to particular sampling methodology and expression analysis methodology used, but the particular methods used in the instantly claimed invention were routinely used to detect gene expression in blood at the time the invention was made, and thus the claimed invention is prima facie obvious in view of the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-36 and 52-68 of copending Application No. 10/989191. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to methods of diagnosing or prognosing schizophrenia or bipolar using steps of determining the expression level of two or more RNA transcripts expressed in blood of individuals, and teaching the use of quantitative RT-PCR in claim 30. The claimed invention is silent as to the status of the blood sample ("unfractionated"), however, at

the time the invention was made it was routine to obtain expression profiles from blood samples without separating cell types, and given the disclosure of the claims of the copending application, this embodiment would have been prima facie obvious. The claims of the copending application are silent as to particular sampling methodology and expression analysis methodology used, but the particular methods used in the instantly claimed invention were routinely used to detect gene expression in blood at the time the invention was made, and thus the claimed invention is prima facie obvious in view of the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-35 of copending Application No. 10/980850. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to methods of diagnosing or prognosing liver cancer using steps of determining the expression level of two or more RNA transcripts expressed in blood of individuals, referring specifically to particularly expressed biomarkers in claims 17-20, and teaching the use of quantitative RT-PCR in claim 26. The claimed invention teaches using whole blood samples and samples from drops of blood (claims 22 and 23), and at the time the invention was made it was routine to obtain expression profiles from blood samples without separating cell types, and given the disclosure of the claims of the copending application, this embodiment would have been prima facie obvious. The claims of the copending application are

silent as to particular sampling methodology and expression analysis methodology used, but the particular methods used in the instantly claimed invention were routinely used to detect gene expression in blood at the time the invention was made, and thus the claimed invention is prima facie obvious in view of the copending claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, and 38-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 26-27, 30-33, and 36-62 of copending Application No. 10/268730. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or obvious in view of, the copending claims. For example, copending claim 26 teaches all of the limitations of instant claim 7, with copending claim 27 anticipating instant claim 8. The claims of the copending application do not teach methods of diagnosis and prognosis as set forth in instant claims 1-6, but since the claims of the copending application specifically set forth that the differently expressed genes are "indicative of disease in said subject" it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods taught in the copending application to diagnose disease. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. Claims 1-10, 13, 16-17, and 19-37 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, and 38-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-31 and 36 of copending Application No. 10/802875. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are directed towards an invention that is a species of the instantly generically claimed invention, namely the identification of genetic markers and the diagnosing or prognosing of coronary artery disease using methods as set forth in the instant claims. For example, claim 1 of the copending application teaches determining the level of one or more gene transcripts in blood obtained from individuals having coronary artery disease, comparing that to one or more individuals not having coronary artery disease, and identifying those genes that have differences as genetic markers for coronary artery disease. The claim does not specifically state that these are genes that are expressed in blood and non-blood tissue, as required by instant claim 7, for example, but this is an inherent property of many of the genes set forth in claim 8 of the copending application (which refers to genes set forth in Table 3L), and further this is provided by the method of claim 13, which depends from each of the independent claims of the copending application. Further, claims 10-12 of the copending application are directed towards methods of diagnosing or prognosing coronary artery disease using gene expression analysis. The copending claims teach using whole blood samples from one or more individuals (claim 14, for example), and teach using quantitative RT-PCR to complete the analysis (claim 19 of the copending application, for example). Regarding the further method limitations of the instant claims, such as claims 28-31, these would have been prima facie obvious over the claims of the copending application in view of the state of the prior art which

teaches methods for completing quantitative PCR methods that include using controls and housekeeping genes to quantify gene expression products.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-57 of copending Application No. 10/809675. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are directed towards an invention that is a species of the instantly generically claimed invention, namely the identification of genetic markers and the diagnosing or prognosing of osteoarthritis using methods as set forth in the instant claims. For example, claim 49 of the copending application teaches determining the level of one or more gene transcripts in blood obtained from individuals having osteoarthritis, comparing that to one or more individuals not having osteoarthritis, wherein a difference in expression indicative of osteoarthritis. The claim does not specifically state that these are genes that are expressed in blood and non-blood tissue, as required by instant claim 7, for example, but this is an inherent property of the genes set forth in claim 49. Further, the claims of the copending application are directed towards methods of diagnosing or prognosing osteoarthritis using gene expression analysis. The copending claims teach using whole blood samples from one or more individuals that have not been fractionated into cell types and are lysed blood samples (claims 50 and 51), and teach using quantitative RT-PCR to complete the analysis (claim 53 of the copending application, for example). Regarding the further method limitations of the instant claims, such as claims 28-31,

these would have been prima facie obvious over the claims of the copending application in view of the state of the prior art which teaches methods for completing quantitative PCR methods that include using controls and housekeeping genes to quantify gene expression products.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. The following statements of rejection are provided without further analysis because they are very similar to the analysis set forth for rejections over applications 10/802875 and 10/809646 in this office action. These additional applications have claimed inventions which differ from one another primarily with regard to disease under study and related genes:

26. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are further provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-57 of copending Application No. 10/812646.

27. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-57 of copending Application No. 10/812702.

28. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812707.

29. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812716.

30. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 61-69 of copending Application No. 10/812731.

31. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-40, 47 and 60 of copending Application No. 10/812737.

32. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-57 of copending Application No. 10/812764.

33. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812777.

34. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812782.

35. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 of copending Application No. 10/812797.

36. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30, 35 and 43 of copending Application No. 10/812827.

37. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/813097.

38. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 49-57 of copending Application No. 10/816357.

39. Claims 1-2, 7-8, 17, 19-21, 23-24, 28-29, 31-34, 38-42, and 44-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33, 38 and 48 of copending Application No. 10/812716.

Response to Remarks

Applicant's remarks regarding the 112 1st paragraph rejection for new matter of claim 9, which limitation is now present in newly added claim 46, are addressed in the statement of rejection of newly added claims 39 and 46.

The previously set forth 112 2nd rejections are overcome by amendment.

The rejection of claims 1-6 under 35 U.S.C. 102(b) as being anticipated by Ditkoff et al. (Surgery, December 1996, Vol. 120, pages 959-965) is WITHDRAWN in view of applicant's amendments to the claims. Claims 3-6 have been canceled, rendering the rejection moot. Claims 1 and 2 have been amended to require the analysis of two or more genes in a sample, and Ditkoff et al. analyze only a single gene.

The rejection of claims 1-10, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26, 27, 32, 33, 34, 35, 36, and 37 under 35 U.S.C. 102(a) and 102(b) as being anticipated by Sharma et al. (WO 98/49342, as cited in IDS) is WITHDRAWN in view of the amendment and/or cancellation of the rejected

claims. Further, no rejection under 103 using Sharma et al. is set forth in this office action. While Sharma et al. generally suggest amplifying cDNA with "appropriate primers" and that "when the sequences of the cDNAs are not known, primers may be directed to regions of the nucleic acid molecules which have been introduced" (p. 12, 3rd ¶), Sharma et al. do not teach or suggest the use of primers or oligonucleotides with predetermined sequences for identifying markers or diagnosing disease. Sharma et al. specifically teach away from any step used for identifying probes that are diagnostic for disease where the step uses a sequence based method. Sharma et al. teach that methods which do not rely on sequence based methods "offer the advantage that probes to be used in the methods of the invention are identified and selected from the entire population of transcripts or cDNA since ***no selection is made before separation***...Thus, the identification of transcripts is not biased towards the selection of particular transcripts from a subset of total transcripts (p. 13, first full ¶; emphasis added)." Given this express teaching by Sharma, there would be no motivation to combine the teachings of Sharma et al. with a reference which suggests the use of certain gene specific primers for the amplification and detection of only a subset of differentially expressed genes. The claims are thus free of the teachings of Sharma et al.

The 103 rejections under Nagai et al. in view of Kephart et al. maintained and applied to the newly amended and added claims. Applicant traverses the rejection. It is agreed that Nagai et al. do not teach the detection of RNA from blood samples that have not been fractionated into cell types. Kephart et al. is applied to provide this teaching. Applicant traverses the rejection providing arguments against the combination beginning on page 26 of the response. Applicant points out that Nagai et al. teach that they isolate "lymphocytes." Nagai et al. isolate the cells by

Ficoll-Paque centrifugation, a process which isolates mononuclear cells consisting of lymphocytes together with some monocytes (see Appendix #2 filed with the remarks, Figure A.23 from Immunobiology (2001)). The text book applicant provides to show that this isolation results in the isolation of PBMC also refers to this process as "Isolation of Lymphocytes," even though it clearly states that the process results in the isolation of mononuclear cells. Thus, no matter the nomenclature used by Nagai et al., the isolation process they undertake results in the isolation of mononuclear cells. Kephart et al. expressly suggest their method as a means for avoiding having to isolate mononuclear cells. Applicant goes to great length to discuss the constituents of cells, pointing out that mononuclear cells make up only a portion of cells in blood that express genes, and state that because of this "A person skilled in the art would not expect that the detection and quantification of RNA products of a gene would be identical as between unfractionated blood cells and lymphocytes and thus would not consider the teachings of Kephart as relevant to the teachings of Nagai (remarks, p. 27)." This is not persuasive because Kephart et al. clearly considered that the results would be similar enough that their method be used instead of methods which require the isolation of mononuclear cells. The fact that there are additional cell types in the blood sample which express genes may add to the background of the assay. The polymerase chain reaction, however, is a powerful assay that can be optimized to detect very low levels of target in a sample. Clearly Kephart et al. expected that one could substitute mRNA isolated from whole blood samples without first isolating mononuclear cells prior to RNA extraction in RT-PCR analysis of since they expressly suggest it. Therefore, applicant's argument that a person skilled in the art would not expect the combination to work is not persuasive.

Applicant further points out that figure 5C demonstrates a difference between the quantity of RNA corresponding to the insulin gene in granulocytes, T-lymphocytes, B-lymphocytes or monocytes. This does not provide evidence, however, that the differential expression observed between the normal and diseased samples in Nagai et al. would have been lost when the reference is combined the very clear suggestive teachings of Kephart et al. The granulocytes have identical expression levels to T-lymphocytes. Since granulocytes make up the majority of mRNA expressing cells, and T-lymphocytes make up another large portion, it is not clear how this provides evidence, even for insulin, that differential expression observed using only PMBC would provide a different pattern than that used with whole blood. Further, the example does not teach what samples are represented in figure 5C, whether it is one person, the disease status of that person, etc., nor does the example demonstrate how this result would widely be applied to all genes. The experiments provided by Nagai et al. are not concerned with absolute levels, but with relative differences between controls and diseased patients. wthat there is a difference between the quantity of RNA corresponding to the insulin gene as found in granulocytes that Kephart recommends isolating RNA from whole blood in place of first isolating mononuclear cells which include both lymphocytes and monocytes.

On page 27 applicant further points out that diminished numbers of lymphocytes have been observed in Parkinson's disease, asserting that it would be unpredictable that the results observed by Nagai et al. would be observed in the presence of other types of expressing blood cells. There is not evidence on the record to support the assertion that the relationship would not be observed in a larger population of cells, and applicant's assertion that it would not be or would not be expected to be is attorney's arguments. As noted above, Kephart et al. clearly

expected that the substitution of mRNA from whole blood would be a reliable substitute for mRNA from peripheral mononuclear cells. The rejection is maintained.

The remarks about Wong et al. 1997 are not addressed because no rejection is set forth in this application in view of this reference.

The double patenting rejections are updated and maintained.

Conclusion

40. No claim is allowed.

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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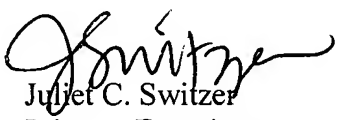

Juliet C. Switzer
Primary Examiner
Art Unit 1634

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